



General

Guideline Title

Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians.

Bibliographic Source(s)

Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P, for the Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2012 Feb 7;156(3):218-31. [134 references] [PubMed](#)

Guideline Status

This is the current release of the guideline.

Regulatory Alert

FDA Warning/Regulatory Alert

Note from the National Guideline Clearinghouse: This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [April 8, 2016 – Metformin-containing Drugs](#) : The U.S. Food and Drug Administration (FDA) is requiring labeling changes regarding the recommendations for metformin-containing medicines for diabetes to expand metformin's use in certain patients with reduced kidney function. The current labeling strongly recommends against use of metformin in some patients whose kidneys do not work normally. FDA concluded, from the review of studies published in the medical literature, that metformin can be used safely in patients with mild impairment in kidney function and in some patients with moderate impairment in kidney function.
- [April 5, 2016 – Diabetes Medications Containing Saxagliptin and Alogliptin](#) : A U.S. Food and Drug Administration (FDA) safety review has found that type 2 diabetes medicines containing saxagliptin and alogliptin may increase the risk of heart failure, particularly in patients who already have heart or kidney disease. As a result, FDA is adding new warnings to the drug labels about this safety issue.

Recommendations

Major Recommendations

The strength of the evidence (high, moderate, low, or insufficient evidence to determine benefits or risks) and strength of recommendations (strong, weak) are defined at the end of the "Major Recommendations" field.

Recommendation 1: *The American College of Physicians (ACP) recommends that clinicians add oral pharmacologic therapy in patients diagnosed with type 2 diabetes when lifestyle modifications, including diet, exercise, and weight loss, have failed to adequately improve hyperglycemia* (Grade: strong recommendation; high-quality evidence).

Initiation of oral pharmacologic therapy is an important approach to effective management of type 2 diabetes. There are no data on the best time to add oral therapies to lifestyle modifications; thus, to avoid an unacceptable burden on patients, other complicating factors should be considered, such as life expectancy of the patient, presence or absence of microvascular and macrovascular complications, risk for adverse events related to glucose control, and patient preferences. The goal for hemoglobin A_{1c} (HbA_{1c}) should be based on individualized assessment of risk for complications from diabetes, comorbidity, life expectancy, and patient preferences. An HbA_{1c} level less than 7% based on individualized assessment is a reasonable goal for many but not all patients.

Recommendation 2: *ACP recommends that clinicians prescribe monotherapy with metformin for initial pharmacologic therapy to treat most patients with type 2 diabetes* (Grade: strong recommendation; high-quality evidence).

The effectiveness, adverse effect profiles, and costs of various oral pharmacologic treatments vary. Metformin is more effective than other pharmacologic agents in reducing glycemic levels and is not associated with weight gain. In addition, metformin aids in decreasing weight and reduces low-density lipoprotein (LDL) cholesterol and triglyceride levels. Metformin was also associated with slightly lower all-cause mortality and cardiovascular mortality compared with sulfonylureas. Finally, metformin is associated with fewer hypoglycemic episodes and is cheaper than most other pharmacologic agents. Therefore, unless contraindicated, metformin is the drug of choice for patients with type 2 diabetes, in addition to lifestyle modification. Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart failure, and any condition that might lead to lactic acidosis.

Physicians and patients should discuss adverse event profiles before selecting a medication. Compared with baseline values, most diabetes medications (metformin, thiazolidinediones, and sulfonylureas) reduced baseline HbA_{1c} by about 1 percentage point 3 or more months after the initiation of treatment. For adverse effects, metformin is associated with an increased risk for gastrointestinal side effects, sulfonylureas and meglitinides are associated with an increased risk for hypoglycemia, and thiazolidinediones are associated with an increased risk for heart failure (with no conclusive evidence for an increase in ischemic cardiovascular risk). However, in comparing the effectiveness of various agents, the evidence shows that metformin is the most efficacious agent as monotherapy and in combination therapy.

Recommendation 3: *ACP recommends that clinicians add a second agent to metformin to treat patients with persistent hyperglycemia when lifestyle modifications and monotherapy with metformin fail to control hyperglycemia* (Grade: strong recommendation; high-quality evidence).

All dual-therapy regimens were more efficacious than monotherapies in reducing the HbA_{1c} level in patients with type 2 diabetes by about 1 additional percentage point. Combination therapies with more than 2 agents were not included in the evidence review. No good evidence supports one combination therapy over another, even though some evidence shows that the combination of metformin with another agent generally tends to have better efficacy than any other monotherapy or combination therapy. However, combination therapies are also associated with an increased risk for adverse effects compared with monotherapy. Generic sulfonylureas are the cheapest second-line therapy; however, adverse effects are generally worse with combination therapies that include a sulfonylurea.

Although this guideline addresses only oral pharmacological therapy, patients with persistent hyperglycemia despite oral agents and lifestyle interventions may need insulin therapy.

Definitions:

The American College of Physicians' Guideline Grading System*		
Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak

Moderate The American College of Physicians' Guideline Grading System*	Strong Strong	Weak Weak
Quality of Evidence	Strength of Recommendation Insufficient evidence to determine net benefits or risks	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden

*Adopted from the classification developed by the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) workgroup.

Clinical Algorithm(s)

None provided

Scope

Disease/Condition(s)

Type 2 diabetes mellitus

Guideline Category

Treatment

Clinical Specialty

Endocrinology

Family Practice

Internal Medicine

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To present the evidence and provide clinical recommendations on the comparative effectiveness and safety of type 2 diabetes medications

Target Population

Adults with type 2 diabetes

Interventions and Practices Considered

1. Treatment with metformin when lifestyle changes fail to control hyperglycemia
2. Treatment with metformin plus a second agent* when monotherapy provides inadequate control

Note: Secondary agents include thiazolidinediones, sulfonylureas, dipeptidyl peptidase-4 (DPP-4) inhibitors, meglitinides, and glucagon-like peptide-1 (GLP-1) inhibitors.

Major Outcomes Considered

- All-cause mortality
- Changes in hemoglobin A_{1c} levels
- Cardiovascular morbidity and mortality
- Weight change
- Cerebrovascular morbidity
- Changes in plasma lipid levels
- Incidence of neuropathy, nephropathy, retinopathy
- Adverse effects of treatment

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Searches of Unpublished Data

Description of Methods Used to Collect/Select the Evidence

The literature search included studies identified by using MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials. The studies that were selected included observational studies and trials published in the English language from 1966 through April 2010. In addition, the MEDLINE search was updated to December 2010 for long-term clinical outcomes (all-cause mortality, cardiovascular morbidity and mortality, cerebrovascular morbidity, nephropathy, neuropathy, and retinopathy). Reference lists, US Food and Drug Administration (FDA) medical reviews, European Public Assessment Reports, Health Canada Product Monographs, unpublished data from pharmaceutical companies, and public registries of clinical trials were also reviewed.

Number of Source Documents

Not stated

Methods Used to Assess the Quality and Strength of the Evidence

Weighting According to a Rating Scheme (Scheme Given)

Rating Scheme for the Strength of the Evidence

This guideline rates the evidence and recommendations by using the American College of Physicians (ACP) guideline grading system, which is based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system (see the "Rating Scheme for the Strength of the Recommendations" field).

Methods Used to Analyze the Evidence

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Standardized forms were used for data abstraction, and each article underwent double review. Quality of randomized, controlled trials (RCTs) was assessed by using the Jadad criteria, and quality of observational studies was assessed as recommended in the Guide for Conducting Comparative Effectiveness Reviews. The I^2 statistic was used to determine study heterogeneity. Further details about the methods and inclusion and exclusion criteria applied in the evidence review are available in the full Agency for Healthcare Research and Quality (AHRQ) report (see the "Availability of Companion Documents" field).

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

The evidence report informing this guideline reviewed data for 11 US Food and Drug Administration (FDA)-approved, unique classes of drugs for the treatment of hyperglycemia in type 2 diabetes (see Appendix Table 1 in the original guideline document). This guideline is based on a systematic evidence review that addressed the following key questions:

- Key question 1: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options for the intermediate outcomes of glycemic control (in terms of hemoglobin A_{1c} [HbA_{1c}]), weight, or lipids?
- Key question 2: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative effectiveness of these treatment options in terms of the following long-term clinical outcomes: all-cause mortality, cardiovascular mortality, cardiovascular and cerebrovascular morbidity (for example, myocardial infarction and stroke), retinopathy, nephropathy, and neuropathy?
- Key question 3: In adults aged 18 years or older with type 2 diabetes mellitus, what is the comparative safety of these treatment options in terms of the following adverse events and side effects: hypoglycemia, liver injury, congestive heart failure, severe lactic acidosis, cancer, severe allergic reactions, hip and nonhip fractures, pancreatitis, cholecystitis, macular edema or decreased vision, and gastrointestinal side effects?
- Key question 4: Do safety and effectiveness of these treatment options differ across subgroups of adults with type 2 diabetes, in particular for adults aged 65 years or older, in terms of mortality, hypoglycemia, and cardiovascular and cerebrovascular outcomes?

The systematic evidence review was conducted by the Johns Hopkins Evidence-based Practice Center. This review updates a 2007 systematic review on the same topic and focuses on head-to-head comparisons rather than placebo-controlled trials.

This guideline rates the recommendations by using the American College of Physicians (ACP) guideline grading system, which is based on the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) system. Details of the ACP guideline development process can be found in ACP's methods paper. This guideline focuses on results that were statistically significant, and details on non-statistically significant results are available in the full Agency for Healthcare Research and Quality (AHRQ) report (see the "Availability of Companion Documents" field).

Rating Scheme for the Strength of the Recommendations

The American College of Physicians' Guideline Grading System*		
Quality of Evidence	Strength of Recommendation	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
High	Strong	Weak

Moderate	Strong	Weak
The American College of Physicians' Guideline Grading System*		
Low Quality of	Strong Strength of Recommendation	Weak
Evidence	Insufficient evidence to determine net benefits or risks	
	Benefits Clearly Outweigh Risks and Burden or Risks and Burden Clearly Outweigh Benefits	Benefits Finely Balanced With Risks and Burden
*Adopted from the classification developed by the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) workgroup.		

workgroup.

Cost Analysis

A formal cost analysis was not performed and published cost analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was approved by the American College of Physicians (ACP) Board of Regents on 19 November 2011.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of supporting evidence is identified and graded for each recommendation (see the "Major Recommendations" field).

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Appropriate pharmacologic treatment of patients with type 2 diabetes mellitus

Potential Harms

Adverse effects of medications

Contraindications

Contraindications

- Metformin is contraindicated in patients with impaired kidney function, decreased tissue perfusion or hemodynamic instability, liver disease, alcohol abuse, heart failure, and any condition that might lead to lactic acidosis.
- Thiazolidinediones are associated with an increased risk for heart failure, and both rosiglitazone and pioglitazone are contraindicated in patients with serious heart failure.

Qualifying Statements

Qualifying Statements

- Clinical practice guidelines are "guides" only and may not apply to all patients and all clinical situations. Thus, they are not intended to override clinicians' judgment.
- The authors of this article are responsible for its contents, including any clinical or treatment recommendations. No statement in this article should be construed as an official position of the U.S. Department of Veterans Affairs.

Implementation of the Guideline

Description of Implementation Strategy

An implementation strategy was not provided.

Implementation Tools

Mobile Device Resources

Patient Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Living with Illness

IOM Domain

Effectiveness

Patient-centeredness

Safety

Identifying Information and Availability

Bibliographic Source(s)

Qaseem A, Humphrey LL, Sweet DE, Starkey M, Shekelle P, for the Clinical Guidelines Committee of the American College of Physicians. Oral pharmacologic treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. *Ann Intern Med.* 2012 Feb 7;156(3):218-31. [134 references] [PubMed](#)

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2012 Feb 7

Guideline Developer(s)

American College of Physicians - Medical Specialty Society

Source(s) of Funding

American College of Physicians

Guideline Committee

Clinical Guidelines Committee

Composition of Group That Authored the Guideline

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Financial Disclosures/Conflicts of Interest

Any financial and nonfinancial conflicts of interest of the group members were declared, discussed, and resolved. A record of conflicts of interest is kept for each Clinical Guidelines Committee meeting and conference call and can be viewed at

www.acponline.org/clinical_information/guidelines/guidelines/conflicts_cgc.htm . Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M11-2857 .

Guideline Status

This is the current release of the guideline.

Guideline Availability

Electronic copies: Available from the [Annals of Internal Medicine Web site](#) .

Print copies: Amir Qaseem, MD, PhD, MHA, American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106; e-mail, aqaseem@acponline.org.

Availability of Companion Documents

The following are available:

- Qaseem A, Snow V, Owens DK, Shekelle P. The development of clinical practice guidelines and guidance statements of the American College of Physicians: summary of methods. Ann Intern Med. 2010 Aug 3;153(3):194-199. Electronic copies: Available from the [Annals of Internal Medicine Web site](#) .
- Bennett WL, Maruthur NM, Singh S, Segal JB, Wilson LM, Chatterjee R, et al. Comparative effectiveness and safety of medications for type 2 diabetes: an update including new drugs and 2-drug combinations. Ann Intern Med. 2011;154:602-13. Electronic copies: Available from the [Annals of Internal Medicine Web site](#) .
- Bennett WL, Wilson L, Bolen S, Maruthur NM, Singh S, Chatterjee R, et al. Oral diabetes medications for adults with type 2 diabetes: an update. Rockville, MD: Agency for Healthcare Research and Quality; 2011. Electronic copies: Available from the [Agency for Healthcare Research and Quality \(AHRQ\) Web site](#) .

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

A collection of Recommendation Summaries for all current American College of Physicians Clinical Guidelines is now available for Personal Digital Assistant (PDA) download from the [American College of Physicians Web site](#) .

Patient Resources

The following is available:

- Summaries for patients. Oral drug treatment of type 2 diabetes mellitus: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2012 Feb 7;156:218-231. Electronic copies: Available from the [Annals of Internal Medicine Web site](#) .

Print copies: Available from the American College of Physicians (ACP), 190 N. Independence Mall West, Philadelphia PA 19106-1572.

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NGC Status

This NGC summary was completed by ECRI Institute on March 30, 2012. This summary was updated by ECRI Institute on April 4, 2014 following the U.S. Food and Drug Administration (FDA) advisory on Rosiglitazone-containing Diabetes Medicines. This summary was updated by ECRI Institute on September 15, 2015 following the U.S. Food and Drug Administration (FDA) advisory on DPP-4 Inhibitors for Type 2 Diabetes. This summary was updated by ECRI Institute on April 12, 2016 following the U.S. Food and Drug Administration (FDA) advisory on Diabetes Medications Containing Saxagliptin and Alogliptin. This summary was updated by ECRI Institute on April 15, 2016 following the U.S. Food and Drug Administration advisory on Metformin-containing Drugs.

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